2

GERIATRIC ANESTHESIA

*Christopher J. Jankowski, MD; David J. Cook, MD**

With the aging of the US population, issues related to surgical care of older patients have considerable public health significance. The elderly age group requires health care resources at a per capita rate that is higher than for any other age group. Perioperative care of older patients generates a variety of challenges. Age-related disease and declining physiologic functional reserve limit the ability of elderly surgical patients to withstand the stresses of anesthesia, surgery, and recovery. Elderly surgical patients have more perioperative complications than younger patients. [1] Complicating the issue is the difficulty of establishing the functional reserve of the older patients because of deconditioning, age-related disease, and cognitive impairment. Even determining who is an appropriate surgical candidate can be difficult. Further, the paucity of well-designed, definitive research concerning elderly surgical patients has provided clinicians with little guidance.

The chapter on geriatric anesthesia in *New Frontiers in Geriatrics Research* noted that geriatrics issues affect all areas of anesthesiology: preoperative evaluations, intraoperative management, postoperative care, and chronic pain management. [2] The chapter began with a review of age-related physiologic changes in the nervous, cardiovascular, respiratory, and urinary systems (see *New Frontiers*, pp. 10–14). In addition, it provided a synopsis of alterations in pharmacokinetics and pharmacodynamics seen in the elderly patient (see p. 14). This information provided a framework for the discussion of existing research and the development of recommendations for needed research. The result was 41 agenda items pertinent to anesthesiology, management of pain, and the perioperative care of the elderly patient. In addition, three issues were defined as Key Questions:

> ***Anes KQ1***: **What preoperative assessments are useful in developing patient management plans for surgeries common in the elderly population?**
>
> ***Anes KQ2***: **Can proper choice of postoperative analgesic techniques reduce postoperative morbidity or improve functional status at discharge?**
>
> ***Anes KQ3***: **How can postoperative pulmonary complications in the elderly patient be reduced?**

The Key Questions specifically address the pre- and postoperative care of the older patient. The literature reviewed for *New Frontiers* suggested that there is no substantive difference in outcome between general anesthesia and regional anesthesia. It has been argued that this is the most significant choice anesthesiologists can make regarding intraoperative care. Thus, investigations regarding other intraoperative management issues were thought likely to be of low yield. Given limited research funding, the decision was made to focus the research agenda on areas more likely to be fruitful.

* Jankowski: Assistant Professor of Anesthesiology, Mayo Clinic, Consultant in Anesthesiology, Mayo Clinic, Rochester, MN; Cook: Professor of Anesthesiology, Mayo Clinic and Foundation, Rochester, MN.

This review updates the literature review of *New Frontiers* and identifies progress since the initial review of 2004. It also addresses emerging areas of research that warrant further investigation with regard to the perioperative care of the elderly person. *New Frontiers* laid out a broad agenda for research into issues of perioperative care of elderly surgical patients. That several of the questions have yet to be answered is not discouraging. To be answered satisfactorily, many of the issues require large multicenter clinical trials. Several years are required to conceive and design such trials, obtain funding, collect and analyze data, and publish the results. Thus, the number of publications addressing items in the research agenda put forward in *New Frontiers* is encouraging. It indicates that researchers already are aware of areas requiring more investigation.

This update identifies two emerging areas that require further study: perioperative glucose control and the role of intra- and postoperative anesthetic and analgesic management, specifically, regional versus general anesthesia. Two new agenda items have therefore been added to the research agenda in geriatric anesthesiology. (See the section New Horizons in Geriatric Anesthesia at the end of the chapter.)

As more data regarding these and issues previously identified by the project become available, information can be incorporated into clinical pathways aimed at improving medical and functional outcomes in elderly surgical patients. Anesthesiologists are involved throughout the continuum of care for every older surgical patient and will have a key role in investigating and implementing interventions to ensure that older patients have optimal surgical outcomes.

METHODS

A literature search was performed on the National Library of Medicine's PubMed database in July 2005. *Anesthesiology* and *intraoperative care* were searched as major MeSH headings and combined with various MeSH terms denoting advanced age: *age*, *geriatric assessment*, *aged*, *aged 80 and over*, *frail elderly*, *longevity*, and *geriatrics*. The following limits were placed on all searches: aged: 65+ years, the English language, humans, and the years 2000–2005. The anesthesiology portion of the search yielded 62 articles, and the intraoperative care segment resulted in 200 articles.

A separate search of the PubMed database was performed in June 2005. In this search, the topic *anesthesiology* was combined with the following terms for advanced age: *65 or older*, *aged*, and *geriatric*. Limits placed on the search included: the English language, core clinical journals, and the years 2000–2005. This search located 107 articles.

Additionally, reference lists from review articles included in the search results were examined for relevant articles.

Finally, separate searches were performed for each individual agenda item, using appropriate search terms and limiting the search as described.

All articles obtained in the various search strategies were reviewed to determine their relevance to the research agenda set forth in the 41 agenda items and three Key Questions in the anesthesiology chapter of *New Frontiers*. Papers that are relevant to the research agenda are briefly summarized herein, and recommendations are made as to whether any original agenda items need to be altered or omitted in light of recent findings.

PROGRESS IN PREOPERATIVE ASSESSMENT OF THE ELDERLY PATIENT

RISK ASSESSMENT

See *New Frontiers,* pp. 16–17.

FUNCTIONAL ASSESSMENT

See *New Frontiers,* pp. 17–18.

PREOPERATIVE TESTING

See *New Frontiers,* pp. 18–21.

PREOPERATIVE OPTIMIZATION

See *New Frontiers,* p. 21.

THE PREOPERATIVE RESEARCH AGENDA

Anes 1 (Level B): **Prospective epidemiologic studies are needed to describe the relative frequency of various outcomes characteristic of older surgical patients for the most common types of surgery.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: This question remains vital. Descriptions of the outcomes of older surgical patients will be the cornerstone for the design, testing, and implementation of strategies for appropriate preoperative evaluation of and intervention for aged patients (see Anes 3).

Anes 2 (Level B): **Once better understanding of characteristic outcomes of specific types of surgery for older patients is attained, patient- and surgery-specific risk factors for geriatric complications should be identified by multivariate analysis that would stratify surgical risk as low, intermediate, or high, depending on type of surgery.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Anes 2 should remain on the research agenda. Information obtained from these types of studies will be invaluable in the design, testing, and implementation of preoperative testing and interventional strategies for improving outcome in geriatric surgical patients.

Anes 3 (Level B): **The positive predictive value of preoperative assessment instruments should be determined in prospective nonrandomized or prospective cohort trials.**

New Research Addressing This Question: The ongoing growth of the elderly age group has serious implications for preoperative evaluation clinics. Elderly patients are the most frequent users of surgical services and often require more extensive preoperative evalua-

tion than younger patients having equivalent procedures. Thus, the challenge is to evaluate increasing numbers of patients needing relatively thorough examinations in a manner that is both cost-efficient and able to correctly identify conditions that may influence perioperative management. The use of questionnaires is one method by which this may be achieved. Ideally, these instruments could differentiate between patients whose medical status dictates a detailed preoperative medical evaluation and those who require a less extensive evaluation. Patients identified as needing an extensive preoperative work-up could be referred directly to a physician. Others could be sent first to a midlevel provider and referred to a physician only if pertinent issues were identified.

Hilditch et al developed a screening questionnaire to determine which patients need to be evaluated by an anesthesiologist before the day of surgery. The 17-question instrument contained closed-end questions regarding general health, exercise tolerance, family history, and previous anesthetic history. Patient responses to the items in the questionnaire were compared with the history obtained by an anesthesiologist. All questions except those regarding kidney disease and previous personal and family anesthetic history had at least good validity as determined by κ-coefficients or percentage agreement with the anesthesiologist's assessment, or both. [3]

Another approach to preoperative evaluation is to have allied health personnel screen patients to determine those who need to be examined by an anesthesiologist before going to surgery. A study by van Klei et al assessed the accuracy of specially trained nurses in preoperative health assessment. In this study, experienced postanesthesia care unit nurses received training in medical history taking and physical examination and attended lectures on a variety of medical subjects related to perioperative care, including those concerning the elderly patient. Patients (N = 4540) were first assessed by a trained nurse and then by an anesthesiologist. The nurses were asked to determine whether a patient was ready for surgery or required further evaluation. The nurse's assessment was compared with that of the anesthesiologist. Nurses were able to identify patients who were not ready for surgery with a sensitivity of 83% (95% confidence interval [CI]: 79% to 87%), a specificity of 87% (86% to 88%), a positive predictive value of 34% (31% to 38%), and a negative predictive value of 98% (98% to 99%). Therefore, although nurses often incorrectly identified patients as being not ready for surgery and referred them for further evaluation when none was needed, they rarely incorrectly classified patients requiring more extensive work-up as being ready for surgery. Although there was some inefficiency to this approach (anesthesiologists still needed to see patients who needed minimal assessment), it nonetheless provided for more efficient resource utilization than the traditional model by eliminating the need for a physician-conducted preoperative evaluation in certain patients. Most importantly, patients who required physician-conducted preoperative examinations rarely were misidentified. [4]

Given the importance of malnutrition in predicting adverse surgical outcomes, [5] it is vital to preoperatively identify malnourished patients, since this information may influence surgical decision making. [6] The Mini Nutritional Assessment (MNA) tool can be used to evaluate nutritional status during a preoperative evaluation. [7–9] However, because it requires anthropomorphic measurements and the completion of a questionnaire, it is time-consuming and may not be appropriate in the setting of a focused preoperative examination. The Mini Nutritional Assessment–Short Form (MNA–SF) consists of six items extracted from the original MNA: five questions and body mass index. [10] The MNA–SF

can be administered quickly and has a sensitivity and specificity of 100% and 69.5%, respectively, for determining the absence of overt malnutrition in elderly surgical patients. Although the positive predictive value is only 19.4%, the negative predictive value was 100% (if the MNA–SF is negative, the patient does not have overt malnutrition). [11]

Modification of This Question in Light of New Research: The MNA–SF successfully identifies patients with overt malnutrition. Given that this condition may alter surgical planning, [6] it would be reasonable to evaluate the MNA–SF in a prospective trial to determine whether its application improves perioperative outcomes in older surgical patients (see Anes 4).

The Hilditch questionnaire and nurse evaluation studies are encouraging. However, neither approach focused on the elderly age group. Given the complexity of older surgical patients, these instruments need to be validated in elderly cohorts. Further, taken together, the results of the two studies suggest that a third approach may be viable: the use of a questionnaire to triage patients requiring extensive evaluation directly to a physician. Others would be seen by a midlevel provider and referred to a physician only if relevant issues were identified. Therefore, Anes 3 should neither be modified nor eliminated.

***Anes 4 (Level A)*: Following evaluation of preoperative assessment instruments (Anes 3), prospective randomized trials should be performed to determine whether the application of these metrics could improve outcomes for elderly surgical patients by altering perioperative intervention, surgical timing, the type or extent of surgery, or postoperative management.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Development of instruments described in Anes 3 will be beneficial only if they result in interventions to improve outcomes. Therefore, Anes 4 should remain unchanged.

***Anes 5 (Level B)*: Prospective cohort studies are needed to determine whether assessment of the older surgical patient's preoperative functional status affects surgical decision making or perioperative care.**

New Research Addressing This Question: A prospective cohort study of 544 patients examined the relative contributions of preoperative health status and intraoperative factors on the incidence of complications in older surgical patients. Multivariate analysis demonstrated that decreased functional status (defined as ≥ 3, where 1 = no limitation of activities, 2 = intermittent limitation, 3 = mild limitation, 4 = moderate limitation, and 5 = severe limitation) is an independent risk factor for adverse postoperative neurologic events. [12] In a prospective cohort study of elderly patients having hip and knee arthroplasty, even subtle declines in preoperative functional status was found to predict postoperative delirium. [13] However, our search strategy uncovered no studies addressing whether baseline functional status affects surgical decision making or perioperative care. No specific recommendations regarding functional status of the heart, pulmonary system, kidneys, mobility, or cognitive status are yet available.

Modification of This Question in Light of New Research: No modification of Anes 5 is recommended. Altering surgical care in light of predictors of adverse outcome is a reasonable approach to the care of older surgical patients. The advent of newer, less invasive alternatives to traditional open procedures offers options where none were previously available. [14] Assessing whether preoperative functional status leads to alterations in perioperative care lays a foundation for the studies proposed in Anes 6. In addition, studies proposed in Anes 5 will provide a measure of the value that those involved in the surgical decision-making process and providing perioperative care place on functional assessment. If the predictive value of functional status on perioperative outcomes is shown not to be appreciated, there will be opportunities to improve care through educational efforts emphasizing its importance.

Anes 6 (Level A): **Depending on findings of prospective cohort studies (Anes 5), randomized trials should be performed to determine whether preoperative functional status assessment of elderly patients changes decisions about type or timing of surgery, or pre- or postoperative care strategies and outcomes.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: In an era of limited health care resources, studies such as those suggested by Anes 6 are vitally important. As more options for less invasive surgical procedures evolve (see Anes 5), selecting the correct procedure for a given patient will become more complicated. A key public health issue will be to select procedures in order to maximize improvement in functional status while minimizing the risk of complications and resource utilization. For example, is there a level of preoperative functional status at which the risk of complications for a given orthopedic procedure is sufficiently high such that it would better to perform a less invasive or temporizing procedure? Conversely, is there a subgroup of patients for whom more heroic operations are indicated? The goal of these studies would be to quantify this information for various elderly surgical populations and develop metrics that would enable surgical decision making to relate more directly to current and predicted functional status.

Anes 7 (Level B): **Cross-sectional or prospective cohort studies are needed to determine by multivariate analysis whether there is an association between pre-existing cognitive impairment, depression, or alcohol abuse and adverse outcomes in geriatric patients.**

New Research Addressing This Question: It is well known that significant pre-existing cognitive impairment, depression, or alcohol abuse predict delirium in elderly medical patients. [15,16] Alcohol abuse and significant cognitive impairment also predict postoperative delirium in elderly noncardiac surgical patients. [17] However, these issues have not been extensively studied in elderly surgical patients. This is important because, unlike medical patients, older surgical patients are generally not acutely ill at the time of surgery. Also, the physiologic stresses imposed by anesthesia and surgery differ from those of medical illness. Thus, studies in this area are essential.

A prospective cohort study examining predictors of postoperative delirium in 427 elderly total hip and total knee arthroplasty patients demonstrated that even subtle preopera-

tive cognitive impairment predicts postoperative delirium. Forty six (10.8%) developed postoperative delirium. Preoperative verbal intelligence as measured by the American National Adult Reading Test [18] and gross cognitive status as measured by the Mini-Mental State Examination (MMSE) [19] were similar between those who did and did not develop postoperative delirium. However, as a group, patients who subsequently developed postoperative delirium were found to have decreased verbal fluency (as measured by the Controlled Oral Word Association Test [20]), verbal learning (as measured by the Auditory Verbal Learning Test [21]), and concentration (as measured by the Stroop Color-Word Test [22]). [13] Gruber-Baldini et al performed a multicenter longitudinal cohort study in 674 elderly hip fracture patients that examined the outcomes associated with cognitive impairment. This group found that that prefracture or in-hospital cognitive impairment as indicated by an MMSE score lower than 24 or the presence of delirium predicted poor functional outcome at 2 and 12 months postoperatively. In addition, incident cognitive dysfunction predicted later functional and social impairment. [23]

Modification of This Question in Light of New Research: Although these studies provide some guidance with regard to cognitive impairment, further work needs to be done to make sure that the results are applicable across a wide range of surgical procedures. In addition, further research is required to determine which tests are most useful for the preoperative evaluation of cognitive function (see Anes 33). Finally, given the prevalence of depression and alcohol abuse in the elderly age group, it is vital to examine the role they play in postoperative outcomes. [24–30]

> ***Anes 8 (Level A)*: For any association that is established by cross-sectional cohort studies between cognitive impairment, depression, or alcohol abuse and adverse outcomes in elderly surgical patients (Anes 7), prospective randomized trials should be performed to determine the effect of pre- or postoperative interventions on these adverse outcomes.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: No modification of Anes 8 is recommended.

PROGRESS IN INTRAOPERATIVE MANAGEMENT

REGIONAL VERSUS GENERAL ANESTHESIA

See *New Frontiers*, pp. 23–25.

PHYSIOLOGIC MANAGEMENT

See *New Frontiers*, pp. 25–26.

THE INTRAOPERATIVE RESEARCH AGENDA

> ***Anes 9 (Level B)*: Cross-sectional or retrospective case-control studies are needed to identify the incidence of adverse cardiac or**

thrombotic-embolic complications in elderly patients undergoing surgery with and without preoperative β-blockade, antithrombotic or antiplatelet therapy, or with a hematocrit above a target value. These studies should be in surgeries identified as having an intermediate or high risk for related complications.

New Research Addressing This Question: A large multicenter prospective observational study addressed the effects of perioperative aspirin for patients undergoing coronary artery bypass grafting. Aspirin (650 mg) administered within 48 hours after revascularization was found to be independently associated with a lower incidence of death, nonfatal myocardial infarction, stroke, renal failure, and bowel infarction. Multivariate analysis did not reveal any other factors to be associated with the reductions of these adverse outcomes. In addition, discontinuation of aspirin use before surgery was found to be an independent risk factor for mortality (odds ratio [OR] = 1.79, 95% CI: 1.18 to 2.69). The risk of hemorrhage, gastritis, infection, and impaired wound healing was not increased with aspirin use. [31]

No studies addressing the issue of perioperative aspirin therapy in a noncardiac surgical population were identified.

A number of previously published prospective studies demonstrate an association between perioperative β-blockade and improved cardiac outcomes, particularly in high-risk patients undergoing high-risk procedures. [32–35] However, in a recent large retrospective study involving nearly 800,000 patients, perioperative β-adrenergic blockade was found to be associated with an increase in in-hospital mortality in patients who had a low a priori risk of cardiac morbidity and mortality (OR = 1.43, 95% CI: 1.29 to 1.58) (see Figure 2.1). [36] Ongoing studies will refine understanding of the role of perioperative β-blockade in elderly surgical patients. [37–39]

To receive a copy of Figure 2.1, please contact Ellen Baumritter at ebaumritter@americangeriatrics.org

Postoperative thromboembolic complications are common and an area of active study (see Anes 10). A retrospective case-control study demonstrated that enoxaparin is superior to warfarin monotherapy for early venous thromboprophylaxis following hip and knee arthroplasty in postmenopausal women (OR 8.6, $P < .0001$ for any thrombosis, OR 11.3, $P < .0001$ for proximal thrombosis). [40] However, in another retrospective case-control study, thomboprophylaxis with tinzaparin was found to be associated with an increased incidence of serious postoperative bleeding. [41] Thus, although low-molecular-weight heparins may be more effective than warfarin therapy in preventing venous thromboembolism, they carry the risk of hemorrhagic complications. Multimodal thromboprohylaxis may offer a way to minimize thrombotic complications and bleeding associated with prophylactic measures. In a large retrospective case series, extensive multimodal thromboprophylaxis (preoperative discontinuation of procoagulant medications, autologous blood donation, hypotensive epidural anesthesia, intravenous heparin during surgery and before femoral preparation, aspiration of intramedullary contents, pneumatic compression, thigh-high stockings, early mobilization, and chemoprophylaxis with aspirin or warfarin for 4 to 6 weeks postoperatively) decreased the incidence of thrombosis and pulmonary embolism in hip arthroplasty patients in comparison with historical controls. [42]

No studies were identified regarding hematocrit value.

Modification of This Question in Light of New Research: There is little question that in high-risk patients undergoing high-risk surgery, perioperative β-blockade reduces adverse cardiac outcomes. Extant studies will help determine its role in patients with lower risk. [37–39]

Perioperative antiplatelet therapy in the form of aspirin has a salutary effect on patients undergoing coronary artery bypass grafting. However, the role of aspirin and other antiplatelet therapy in elderly noncardiac surgical patients still needs to be defined.

Although the efficacy and safety of various antithrombotic strategies have been studied in large prospective randomized trials (see Anes 10), none focused exclusively on elderly patients. This is significant, given the frequency of polypharmacy in older patients and the drug interactions associated with warfarin. [43] Clearly, there is a need for investigations in this area. In addition to retrospective case-control studies, one option for obtaining hypotheses-generating data might be to perform post hoc analyses on data from the elderly patients who participated in the randomized trials. These studies should examine the incidence of adverse reactions as closely as prevention of thrombosis. Subsequent prospective randomized trials could be designed on the basis of these results. Further, there is a need for well-designed retrospective studies examining the utility of multimodal approaches to thromboprophylaxis. This approach is especially attractive for geriatric patients, given that it minimizes pharmacologic intervention.

Alternative medicines are used by a large proportion of the population, and many are associated with excessive bleeding. [44,45] However, to date, no larger studies have associated them with increased perioperative blood loss, transfusion, or bleeding complications. In an era of limited research funding, investigations into the perioperative implications of the use of these substances should have low priority.

A more appropriate use of research resources might be to examine ways to improve administration of known therapies for preventing thrombotic complications. Despite evidence of their efficacy, they are not used universally. For example, although the Nether-

lands has national guidelines for thromboprophylaxis, compliance is not optimal.[46] Computerized alerts and other systems changes may improve delivery of thromboprophylaxis,[47,48] and there is a need to evaluate the feasibility of broad application of these measures.

Finally, research is still required to determine appropriate target hemoglobin levels in older surgical patients. The American Society of Anesthesiologists Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies states that patients usually should receive transfusions for hemoglobin levels of $\leq$ 6 g/dL and rarely for levels $>$ 10.[49] However, this guideline does not specifically consider elderly patients. Further, higher hemoglobin levels may be beneficial in the elderly patient.[50] Therefore, there is a critical need for studies in this area.

> ***Anes 10 (Level A)***: **For any association in elderly patients of cardiac thrombotic-embolic complications with a specific preoperative therapy or hematocrit level, prospective cohort or randomized studies are needed to determine if pre- or intraoperative therapies would reduce the complications.**

New Research Addressing This Question: A number of recent large prospective randomized trials have examined the efficacy of a variety of thromboprophylactic strategies, including newer agents such as factor Xa and thrombin inhibitors.[51–60] However, as noted (see Anes 9), none focused solely on older patients.

Modification of This Question in Light of New Research: Prospective studies regarding cardiac complications and β-blockers have been completed (see Anes 9).
As noted how-
ever, questions remain. Ongoing studies may clarify the issue.[37–39]

Although there has been active investigation of various thromboprophylactic therapies, these studies have not addressed older patients per se. Therefore, more research is required to assure that these interventions have acceptable risk-benefit ratios in this highly vulnerable population.

Studies regarding hematocrit levels and antiplatelet therapy are still needed.

As a whole, studies suggested by Anes 10 address a broad range of critical issues in elderly surgical patients. Although they will be difficult to design and execute, these studies will provide information that could significantly alter surgical care for older patients.

> ***Anes 11 (Level D)***: **Prospective nonrandomized investigation of the effect of perioperative temperature management on surgical morbidity in the geriatric population is needed. These investigations should be conducted under conditions where either the surgery is physiologically very challenging or the older patient carries a high burden of comorbidity. Cardiac, respiratory, bleeding, and renal outcomes would be the primary focus of these investigations.**

New Research Addressing This Question: The search did not locate any articles that directly addressed Anes 11. However, two studies addressed other outcomes related to perioperative temperature management. In one study, 338 mostly elderly patients were randomized to either aggressive forced-air intraoperative warming therapy or standard care during a variety of noncardiac procedures. Patients who were randomized to aggres-

sive intraoperative warming had relative risk reduction of 46% for the development of pressure ulcers. [61]

In an interesting study, Yucel et al performed a post hoc analysis of a cohort of patients with colorectal cancer who were randomized to normothermic versus hypothermic (34.5°C) temperature management during primary resection. The groups were demographically similar, including information on tumor grade and stage. [62] With up to 9 years of follow-up, there was no difference in cancer-free or overall survival. However, in the original study, hypothermia was associated with increased incidence of infection, decreased wound collagen deposition, and increases in days to first solid food, suture removal, and hospital discharge. [63] Given the strong evidence of other adverse outcomes associated with it, [63–68] the results of this study should not be viewed as an endorsement of perioperative hypothermia. That said, the authors are to be commended for evaluating long-term outcomes associated with perioperative hypothermia. Across the spectrum of geriatric surgical care, more studies addressing the long-term implications of perioperative management are needed.

Modification of This Question in Light of New Research: As noted, no studies have been published directly addressing Anes 11 since *New Frontiers* was published. In addition, recent evidence suggests that advanced age is a risk for developing intraoperative hypothermia. [69] Thus, Anes 11 should remain on the research agenda. However, relevant outcomes should be expanded to include surgical site infections. [63]

> ***Anes 12 (Level D)***: **Retrospective or cross-sectional research studies should be conducted to identify any relationship between the use or timing of perioperative antibiotic therapy and postoperative pneumonia or wound infection. Differences, if any, between younger and older patients undergoing the same type of surgery should also be examined.**

New Research Addressing This Question: A retrospective study examined the effect of intraoperative redosing of prophylactic cefazolin on surgical site infection in cardiac surgery lasting more than 240 minutes after the first dose was given. Most of the 1548 patients were elderly. The overall risk of surgical site infection was similar between those who had intraoperative redosing (9.4%) and those who did not (9.3%) (OR 1.01, 95% CI: 0.70 to 1.47). However, redosing reduced the incidence of surgical site infection in patients whose procedures lasted longer than 400 minutes (7.7% versus 16.0%, OR 0.44, 95% CI: 0.23 to 0.86). [70]

Modification of This Question in Light of New Research: This study is an encouraging start. However, its results may not be generalizable to the noncardiac surgical population. Further, no studies have addressed prophylactic antibiotic use and the risk of pneumonia. Likewise, there have been no studies to determine what, if any, differences exist between younger and older patients. Anes 12 should remain on the research agenda unchanged.

> ***Anes 13 (Level C)***: **Depending on the findings in Anes 12, prospective randomized studies should be used to determine whether preoperative or postoperative antibiotic therapies reduce complications related to infections in elderly surgical patients.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Surgical site infections are a major source of postoperative morbidity and mortality and may be responsible for ~$1.6 billion in excess hospital charges annually in the United States. [71] Determining effective strategies to prevent complications from perioperative infections will have important public health and patient care implications. Anes 13 should not be altered.

Anes 14 (Level D): **Multicenter case-control or prospective cohort studies should be performed to determine whether receiving or not receiving blood in the perioperative period affects the incidence of perioperative infection and immunosuppression in elderly patients. Multivariate analysis would be required to separate the effect of homologous blood transfusion from the comorbid conditions making transfusion more likely.**

New Research Addressing This Question: The search revealed two articles related to Anes 14. The first was a small retrospective analysis of 56 patients undergoing repair of ruptured abdominal aortic aneurysms. Respiratory complications (prolonged ventilation, infection, or respiratory distress) occurred in 40.0% of patients receiving salvaged autologous blood and in 12.5% patients who did not ($P = .047$). However, the analysis did not consider whether this may have been a function of comorbid conditions. Also, 95% of patients who received salvaged autologous blood had suprarenal aortic cross-clamping, compared with only 63% in the group that did not receive salvaged blood. These, among other reasons, limit the applicability of this study to a general elderly surgical population. [72]

The results from the second study may be more broadly applicable. Tang et al performed a single-center prospective cohort study of 2809 patients undergoing elective resection of the colon and rectum to determine the risk factors for surgical site infection. Most patients were older than 56 years. By the use of multivariate analysis, homologous blood transfusion was found to be an independent risk factor for overall surgical infection (OR = 2.0, 95% CI: 1.1 to 3.3 for 1 to 3 units transfused, OR = 6.2, 95% CI: 4.2 to 10.2 for $\geq$ 4 units transfused). Interestingly, of the 14 risk factors found to be significant via multivariate analysis, only blood transfusion was a significant risk factor for all surgical site infections examined (incisional and organ-space with and without anastomotic leakage). [73]

Modification of This Question in Light of New Research: The study by Tang et al is well done. Nevertheless, more research is needed, specifically, studies more closely examining the effects of age and including other populations for whom surgical site infections may be devastating, such as orthopedic and cardiac surgical patients. In addition, the studies must be designed and analyzed with a view toward specific implications for improving practice.

Anes 15 (Level C): **If perioperative infection and immunosuppression in older surgical patients are shown to be associated with receiving blood in the preoperative period (Anes 14), alternative strategies such as delaying surgery or erythropoietin therapy should then be compared with blood transfusion in prospective cohort studies, because a randomized trial could not be justified.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: An aging population places strain on health care resources. Therefore, it is essential to examine simple, inexpensive strategies such as delaying surgery to improve outcome. Anes 15 should remain on the research agenda unchanged.

Anes 16 (Level D): **Cohort or case-control studies are needed to determine the relationship in older surgical patients between perioperative termination of anticoagulation and thromboembolic or bleeding risk.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Given the frequency with which older surgical patients require long-term anticoagulation for mechanical heart valves, chronic congestive heart failure, and history of thrombosis, as well as the variability of perioperative anticoagulant bridging therapy, studies of this nature are imperative. Anes 16 should remain on the research agenda unchanged.

Anes 17 (Level C): **The effect of timing of termination and resumption as well as the temporizing use of antiplatelet agents in older surgical patients should be compared in case-control or prospective cohort studies.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Anes 17 should remain on the research agenda unchanged.

Anes 18 (Level B): **In prospective cohort studies the incidence of perioperative hypotension, aspiration, and renal insufficiency should be compared in elderly patients undergoing standard nothing-by-mouth orders before surgery and in elderly patients who would be allowed clear liquids closer to the time of surgery. This study would need to be conducted in:**

- **patients undergoing specific types of procedures where liberalization of fluid intake is not contraindicated for surgical reasons,**
- **patients undergoing procedures that place them at greater risk for developing hypovolemia (eg, bowel prep), and**
- **instances where preoperative hypovolemia may contribute to complications (eg, angiographic procedures).**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Cardiac catheterizations are common in the United States, and most are performed on elderly patients. Aging is asso-

ciated with both chronic dehydration and reduced creatinine clearance, and these two factors are fundamental determinants of contrast nephropathy.[74] Prevention of contrast nephropathy is an area of active investigation, but those studies have not reached specific conclusions or recommendations regarding care of the elderly patient in angiographic procedures.[74]

In January 1999 the American Society of Anesthesiologist Task Force on Preoperative Fasting issued new guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration.[75] The revised guidelines call for preoperative fasts of 6, 4, and 2 hours for solids, nonclear liquids, and clear liquids, respectively. In theory, the preoperative fast may now have a lesser effect on volume status and may reduce the incidence of perioperative hypotension and renal insufficiency. That said, chronic dehydration is common in the elderly patient; its incidence increases with age, and it is often misdiagnosed.[76–78] Given the frequency of baseline chronic dehydration, it is unlikely that the new preoperative fasting guidelines will have a significant effect on the incidence of hypotension and renal insufficiency. However, there remains need for studies examining this issue. Further, the new guidelines may increase the incidence of aspiration in elderly surgical patients, a group that already is at high risk.[79,80] It is critical that the effect of the new preoperative fasting guideline on the incidence of aspiration be examined.

PROGRESS IN POSTOPERATIVE MANAGEMENT

POSTOPERATIVE RESPIRATORY INSUFFICIENCY

See *New Frontiers,* pp. 28–29.

ACUTE PAIN MANAGEMENT

See *New Frontiers,* p. 29.

PAIN AND ADVERSE OUTCOMES

See *New Frontiers,* pp. 30–32.

DELIRIUM AND COGNITIVE DECLINE

See *New Frontiers,* pp. 32–34.

THE POSTOPERATIVE RESEARCH AGENDA

Anes 19 (Level B): **Prospective studies that better identify patient and procedural risk factors for respiratory failure, aspiration, and pneumonia in elderly surgical patients are needed.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Pulmonary complications are common after surgery.[81,82] Although patient and procedural risk factors have been studied, little is known about them in the elderly age group. Recent awareness of the role of obstructive sleep apnea in postoperative pulmonary complications, along with its preva-

lence and the unreliability of traditional markers for the syndrome in the elderly patient, [83,84] make studies suggested by Anes 19 even more important. Therefore, it should remain on the research agenda unchanged.

> ***Anes 20 (Level A)***: **Randomized trials are needed to determine if respiratory monitoring or O_2 therapy can reduce the incidence of respiratory failure in elderly surgical patients.**

New Research Addressing This Question: Though there are ongoing studies addressing this issue, [85] none have been published to date.

Modification of This Question in Light of New Research: The interventions suggested by Anes 20 require little effort or expense. If proved to be effective, they will provide an elegant solution to a significant problem. Therefore, Anes 20 should not be altered or eliminated.

> ***Anes 21 (Level A)***: **Randomized studies of prophylactic antibiotics, changes in pharyngeal instrumentation, or the way feeding is advanced are needed to determine whether practice changes reduce aspiration and postoperative pneumonia in elderly surgical patients. (See also the Key Questions at the beginning of the chapter.)**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Anes 21 should remain on the research agenda unchanged. The trend toward earlier discharge and feeding in abdominal surgery patients makes studies regarding the effects of early advancement of feeding even more pertinent.

> ***Anes 22 (Level B)***: **Cross-sectional studies capable of identifying any relationship in elderly surgical patients between intensive nutritional support in high-risk surgery and functional status on discharge (eg, chronic respiratory failure, ambulation, independent living) are needed.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Functional status may be the most significant outcome measure for elderly surgical patients. Therefore, studies examining the association between perioperative interventions and functional status are especially important. Anes 22 should remain on the research agenda unchanged.

> ***Anes 23 (Level A)***: **Data from studies of associations between nutritional support and postoperative functional status after high-risk surgery in elderly patients (Anes 22) should be used to design prospective cohort or randomized controlled trials comparing feeding strategies in elderly patients at risk for malnutrition and muscle wasting following major surgery.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Anes 23 should remain on the research agenda unchanged.

Anes 24 (Level C): **Randomized trials of interventions that might attenuate postoperative catabolism or facilitate the transition to anabolism in the elderly patient are needed.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Anes 24 should remain on the research agenda unchanged.

Anes 25 (Level C): **Large cross-sectional studies describing analgesic practice and its complications in the elderly surgical patient are needed.**

New Research Addressing This Question: Frasco et al examined the effect of the Pain Initiative of the Joint Commission for Accreditation of Healthcare Organizations (JCAHO) on perioperative analgesic care. [86] The JCAHO Pain Initiative standards recognize that pain is often undertreated in surgical patients and are an attempt to enhance perioperative analgesic care by improving assessment and promoting aggressive treatment of pain. [87] In the Frasco study, 541 patients treated by the use of the JCAHO Pain Initiative guidelines were compared with matched historical controls who had surgery in the period immediately before the JCAHO Pain Initiative was implemented. Mean age (± S.D.) in the treatment group was 63.1 (± 14.3) years and 63.9 (± 13.8) years in the historical controls. However, patients ranged from 15 to 93 years of age. Those whose care was delivered according to the guidelines received more opiates, but also required more treatment for postoperative nausea and vomiting. There was no difference between groups in the incidence of respiratory depression requiring intervention. [86]

Modification of This Question in Light of New Research: Anes 25 should remain on the research agenda unchanged. The study described did not focus on elderly surgical patients. Given the alterations in baseline opiate sensitivity [88,89] and decreases in metabolism and elimination capacity in the elderly patient (see *New Frontiers,* pp. 13–14), the studies suggested in Anes 25 remain vitally important and will form the cornerstone for studies based on Anes 26.

Anes 26 (Level B): **Depending in part on findings of large, descriptive studies of analgesia in elderly patients (Anes 25), prospective cohort studies are needed to determine the effect of analgesic modes (patient-controlled versus as-needed versus scheduled dosing), route of administration, the role of nonopioid adjunctive drugs, and nonpharmacologic interventions. These investigations must define a balance between adequate analgesia and reduction of the incidence of adverse drug events in the elderly patient.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: The information provided by studies related to this question will provide important preliminary data for trials outlined in Anes 27. Anes 26 should remain on the research agenda unchanged.

***Anes 27 (Level A)*: Prospective randomized controlled trials comparing outcomes with analgesic programs specific to types of surgery are needed to determine whether analgesic regimes designed for the elderly patient reduce in-hospital morbidity or improve functional status on discharge. (See also the Key Questions at the beginning of the chapter.)**

New Research Addressing This Question: In a prospective observational study to determine the risk factors for postoperative delirium in elderly patients undergoing total hip and knee arthroplasty, patients whose postoperative analgesic regimen consisted of continuous perineural infusions of local anesthetics supplemented with small amounts of opiates were found to have a 59% lower incidence of postoperative delirium than those who received patient-controlled analgesia intravenous opiates alone. [90] The study did not address the issue of functional status on discharge.

Modification of This Question in Light of New Research: Though the study described was not a randomized trial, its results suggest that investigations in this area may be fruitful. Future trials should be randomized and consider hospital resource utilization and long-term functional status as well as in-hospital morbidity and functional status on discharge. Further, the utility of multimodal analgesic approaches and novel analgesic adjuncts, such as dexmedetomidine, [91,92] should be examined in trials involving operations that are not amenable to regional anesthetic and analgesic techniques.

***Anes 28 (Level D)*: Improved tools for the assessment of pain in the cognitively impaired elderly patient should be developed.**

New Research Addressing This Question: Pain is often inadequately treated in the cognitively impaired elderly patient. [93] It is a subjective experience, and significant cognitive impairment limits patients' abilities to complete self-report measures. [94,95] Therefore, the development of appropriate measures of pain in elderly patients with cognitive impairment is imperative. The challenge is to develop tools that do not rely on self-report of symptoms.

Several new instruments for the assessment of pain in cognitively impaired older patients have been introduced recently. The first is the DOLOPLUS 2. It consists of 10 items across three domains: somatic reactions (somatic complaints, protective body postures at rest, protection of sore areas, expression, sleep pattern), psychomotor reactions (washing and/or dressing, mobility), and psychosocial reactions (communication, social life, and behavioral problems). Although this scale is recommended for use only in noncommunicative patients, several items rely on the patient's ability to communicate. [96] The only validation study for the instrument compared it with the Visual Analog Scale (VAS), a self-report tool. [97] Thus, its utility is unclear.

The Pain Assessment in Advanced Dementia (PAINAD) scale is an observational metric based on five items: breathing, vocalization, facial expression, body language, and consolability. [98] The PAINAD scale was validated in a cohort of severely demented nursing home patients. Reliability (consistency across time and different raters) and validity (ability to measure pain and not other conditions [eg, depression] and to accurately reflect changes in pain experience) are adequate. [99]

Fisher et al developed the Proxy Pain Questionnaire (PPQ) to investigate the association in nursing home patients between caregiver reports and Minimum Data Set (MDS) reports

of pain. [100] The MDS is a quarterly assessment of nursing home patients that evaluates a variety of parameters, including pain. [101,102] The attractiveness of the PPQ lies in its simplicity. It consists of three questions: (1) Within the last week has this resident experienced pain? (2) How often does this resident experience pain? (3) In general, when this patient is in pain, how would you describe the extent of the pain? Despite the straightforward nature of the instrument, it is very reliable. Unfortunately, it was found to be only weakly valid in comparison with the MDS. [99] However, pain may be under-reported by use of the MDS. [103] Thus, further validation is necessary to determine the utility of the PPQ.

The Pain Assessment for the Dementing Elderly (PADE) is another instrument designed for use by non-research-trained staff. It consists of 24 brief questions and takes about 5 minutes to complete. [104] It is highly reliable, but weakly valid. [99]

Modification of This Question in Light of New Research: A key aspect of perioperative care is excellent pain control. Pain is associated with a variety of adverse outcomes. [105–111] Satisfactory postoperative analgesia depends on the ability to assess level of pain. With an aging population, increasing numbers of cognitively impaired patients will require surgery. For these patients, traditional self-reported measures of pain, such as the VAS and the Numeric Pain Scale scores, clearly are inadequate. [112] In addition, existing tools are underutilized. [113] Development of instruments to assess pain in this population is essential. Although the studies described are encouraging, none was tested in a surgical population. Future development of such metrics needs to include postoperative patients in the validation cohort. In addition, when possible, instruments should be designed to be used by caregivers rather than specially trained researchers or clinicians in order to increase vastly the utility of future assessments.

***Anes 29 (Level C)*: Improved tools for assessing pain in cognitively impaired elderly patients (Anes 28) should be used to determine the adequacy of pain management strategies in this group of patients.**

New Research Addressing This Question: As noted in Anes 28, no sufficient tools have been developed.

Modification of This Question in Light of New Research: The use of new tools for evaluating pain in this population to test pain management strategies will be crucial to improving perioperative care in this vulnerable population. Anes 29 should remain on the research agenda unchanged.

***Anes 30 (Level D)*: A retrospective review is needed to determine the incidence of polypharmacy with combinations of drugs that might contribute to complications (hypotension, bradycardia, falls, confusion, bleeding diathesis, constipation, and urinary retention) in geriatric surgical patients.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: The baseline frequency of polypharmacy in the elderly person, [114,115] combined with the large number of medications administered in the perioperative period, makes answering this question important. Anes 30 should not be altered or eliminated.

Anes 31 (Level A): **The effect on outcomes for elderly surgical patients of simplifying drug regimens in hospital or of communicating that information to primary care physicians should be examined in a randomized controlled trial.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Acute hospitalization provides an excellent opportunity to review and appropriately adjust the often complicated medication regimens of elderly surgical patients and thus to minimize the risks associated with polypharmacy. However, a program to do so would require a great deal of effort on the part of health care providers. Therefore, there must be studies evaluating the efficacy of this approach before it is implemented.

Anes 32 (Level B): **Cross-sectional studies, with multivariate analysis, are needed to determine whether the risk factors for delirium in elderly surgical patients are the same as those for elderly medical patients.**

New Research Addressing This Question: A single-center prospective cohort study addressing this issue in elective orthopedic surgical patients has recently been completed. Results are forthcoming. [116]

Modification of This Question in Light of New Research: The ongoing study may clarify this issue. However, further investigations will be necessary to confirm its results and test its applicability across a broad range of elderly surgical patients.

Anes 33 (Level B): **Studies are needed on the utility of the Confusion Assessment Method (CAM) for serial testing of elderly patients before and after surgery to facilitate the diagnosis of postoperative delirium. The CAM should be compared with other tests of cognitive function and with the clinical diagnosis for delirium. At the same time, since dementia is the leading predisposing factor for delirium, the utility of short mental status tests to make the preoperative diagnosis of early dementia should be tested, using a full psychiatric examination as the gold standard.**

New Research Addressing This Question: The literature search did not reveal any studies assessing the utility of the CAM in a purely surgical population. This is significant for two reasons: First, the CAM was developed by the use of patients in a general medicine ward and an outpatient population. [117] Applying the instrument in a surgical population may be difficult. For example, using it in the early postoperative period may identify patients as delirious when they are still under the influence of anesthetic agents. It is unclear whether delirium in that circumstance is prognostic of outcome in the same way as delirium that occurs after the effects of anesthetics have abated. However, there is evidence that, in hip fracture surgery patients, a positive CAM 60 minutes after discontinuation of volatile anesthetic agents predicts later postoperative delirium. [118] And second, the CAM already has been used as the endpoint for a number of studies examining postoperative delirium. [13,17,23,50,90,105,118–137] Without validation and agreement on the appropriate time at which to begin screening for delirium, it is difficult to interpret the findings of studies applying the CAM in surgical patients.

The CAM has been compared with other screening tests for delirium. Gaudreau et al compared the Nursing Delirium Screening Scale (Nu-DESC) with the CAM, the Memorial Delirium Assessment Scale (MDAS), [138] and the criteria from the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV). The Nu-DESC is a brief, five-item observational instrument based on the DSM-IV criteria for delirium. In a comparison with the CAM, the Nu-DESC was found to be 85.7% sensitive and 86.8% specific. However, CAM results, not DSM-IV criteria, were considered the gold standard for the diagnosis of delirium in this study. [139] Adamis et al compared the Delirium Rating Scale, [140] a 10-item clinician-rated symptom rating scale for delirium, with the CAM and found good to very good agreement between the two instruments in acutely ill hospitalized patients, but, again, no gold standard for diagnosis was used for comparison. [141] Other studies have the same methodologic flaw. [142–144]

Regarding preoperative cognitive screening, the MMSE [19] is a widely accepted screen for dementia; however, it is too cumbersome and time-consuming for use in busy clinical practices. Because of this, short tests of cognition have been developed. [145–148] The Mini-Cog is a more recently developed screening tool for dementia and is considered to be among the most useful. [149,150] It consists of three-item recall and a clock-drawing test and is to be performed in 2 to 4 minutes, rather than the 5 to 12 minutes necessary for the MMSE. It is similar in sensitivity and specificity to the MMSE and formal neuropsychologic testing for detecting dementia. [151] No studies were identified that used the Mini-Cog in a surgical population.

Modification of This Question in Light of New Research: There remains a need for studies examining the use of the CAM in elderly surgical patients. Research is needed not only to validate its usefulness in this population but also to determine the optimal time at which to apply it in relation to emergence from anesthesia. Studies comparing other delirium assessment instruments with the CAM must utilize gold standard clinical criteria, such as those in the updated text revision of DSM-IV (the DSM-IV-TR). These projects are essential to improving understanding of issues regarding postoperative delirium because without valid, standardized instruments to determine the presence of delirium, it will be difficult to interpret the results of studies.

Although research into the Mini-Cog is encouraging, there remains a need for further investigation into the utility of this and other instruments for surgical populations.

***Anes 34 (Level A)*: Prospective controlled (nonrandomized; ie, by ward or unit) trials in patients at moderate to high risk for delirium should be performed to determine the effect of preoperative or postoperative interventions on the incidence of delirium.**

New Research Addressing This Question: A longitudinal prospective sequential study examined the effect of a nurse-led interdisciplinary intervention for delirium. [136] The intervention consisted of nursing education, systematic screening for delirium using the NEECHAM Confusion Scale, [152] consultation with a trained geriatric care provider, and use of a scheduled pain medication protocol. A cohort of 60 elderly patients admitted for hip fracture treatment received standard care; 60 subsequent patients (median age 80 years, interquartile range 12 years) received the intervention. The incidence of delirium was similar in the control and intervention cohorts (23.3% versus 20.0%, respectively, $P = .82$). However, the duration of delirium was shorter in the intervention cohort ($P = .03$). Severity of delirium was reduced in the intervention group as well. In addition,

cognitive function measured by the memory subdimension of the MMSE [19] was better in the delirious patients than in the interventional group. Unfortunately, the intervention did not result in improved rehabilitation or functional status.

In a prospective trial Marcantonio et al randomized 126 hip fracture patients to either usual care or to receive a proactive geriatrics consultation. [50] In the intervention group, a geriatrician made daily rounds and made recommendations based on a structured protocol (see Table 2.1). The number of recommendations was limited to five on the initial visit and three in subsequent visits in order to improve compliance. Mental status and incidence and severity of delirium were assessed daily by blinded observers using validated scales. [19,117,138,153,154] The incidence of delirium was reduced in the intervention group (32% versus 50%, $P = .04$, relative risk 0.64, 95% CI: 0.37 to 0.98). Delirium severity was reduced as well. This study is encouraging because the recommendations used for the intervention group could, by and large, be implemented through education of surgical care

***TABLE 2.1*—Content of the Structured Geriatrics Consultation to Prevent Postoperative Delirium**

1. Adequate CNS oxygen delivery:
   a. Supplemental oxygen to keep saturation > 90%, preferably > 95%
   b. Treatment to raise systolic blood pressure > 2/3 baseline or > 90 mmHg
   c. Transfusion to keep hematocrit > 30%
2. Fluid/electrolyte balance:
   a. Treatment to restore serum sodium, potassium, glucose to normal limits (glucose < 300 mg/dL for diabetics)
   b. Treat fluid overload or dehydration as appropriate
3. Treatment of severe pain:
   a. Around-the-clock acetaminophen (1 gram four times daily)
   b. Early-stage breakthrough pain: low-dose morphine, avoid meperidine
   c. Late-stage break-through pain: oxycodone as needed
4. Elimination of unnecessary medicine:
   a. Discontinue/minimize benzodiazepines, anticholinergics, antihistamines
   b. Eliminate drug interactions, adverse effects; modify drugs accordingly
   c. Eliminate medication redundancies
5. Regulation of bowel/bladder function:
   a. Bowel movement by postoperative day 2 and every 48 hours
   b. Discontinue urinary catheter by postoperative day 2, screen for retention or incontinence
   c. Skin care program for patients with established incontinence
6. Adequate nutritional intake:
   a. Dentures used properly, proper positioning for meals, assist as needed
   b. Nutritional supplements as needed
   c. If unable to take food orally, feed via temporary nasogastric tube
7. Early mobilization and rehabilitation:
   a. Out of bed on postoperative day 1 and several hours daily

***TABLE 2.1*—Content of the Structured Geriatrics Consultation to Prevent Postoperative Delirium—Cont'd**

b. Mobilize/ambulate by nursing staff as tolerated
c. Daily physical therapy; occupational therapy if needed

8. Prevention, early detection, and treatment of major postoperative complications:
   a. Myocardial infarction/ischemia—electrocardiogram, cardiac enzymes if needed
   b. Supraventricular arrhythmias/atrial fibrillation—appropriate rate control, electrolyte adjustments, anticoagulation
   c. Pneumonia/chronic obstructive pulmonary disease—screening, treatment, including chest therapy
   d. Pulmonary embolus—appropriate anticoagulation
   e. Screening for and treatment of urinary tract infection

9. Appropriate environmental stimuli:
   a. Appropriate use of glasses and hearing aids
   b. Provision of clock and calendar
   c. If available, use of radio, tape recorder, and soft lighting

10. Treatment of agitated delirium:
   a. Appropriate diagnostic workup/management
   b. For agitation, calm reassurance, family presence, and/or sitter
   c. For agitation, if absolutely necessary, low-dose haloperidol 0.25–0.5 mg every 4 hours as needed; if contraindicated, use lorazepam at same dose

SOURCE: Marcantonio ER, Flacker JM, Wright RJ, et al. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 2001;49:516–522. Adapted and reprinted with permission.

providers and adapted into care protocols for geriatric surgical patients without significant increase of health care resource utilization.

In addition to studies examining altered paradigms of perioperative care for geriatric surgical patients, pharmacologic prevention of delirium has been examined. In a study examining the use of low-dose haloperidol for the prevention of delirium, 430 hip surgery patients $\geq$ 70 years old were randomized to receive 1.5 mg per day of haloperidol or placebo starting preoperatively and continuing for up to 3 days after surgery. [155] Though there was no difference in the incidence of delirium, severity and duration were reduced in those receiving haloperidol. Importantly, hospital length of stay also was reduced (mean difference = 5.5 days, 95% CI: 1.4 to 2.3 days, $P < .001$). Again, this study demonstrates that a relatively simple and inexpensive intervention can markedly influence perioperative outcome.

Modification of This Question in Light of New Research: The studies described show that pre- and postoperative interventions can improve delirium-related outcomes in elderly hip fracture patients. However, they were performed only in hip surgery patients, a group at relatively high risk for postoperative delirium. Further work is required to determine whether these interventions are effective in other high- and moderate-risk surgical populations. In addition, studies are needed that address the relative contribution of each component of multimodal delirium prevention programs, such as those in the studies by Marcantonio and Milisen. [135,136] Subsequent studies can examine the efficacy of opti-

mized multimodal protocols that are based on projects identifying the most effective individual interventions for preventing delirium. Finally, it is crucial to assess whether the recommendations provided by the geriatric consultation service in the Marcantonio study can be successfully incorporated into the routine care of geriatric surgical patients without the necessity of separate geriatric consultation. This goal is especially important, given the increasing numbers of older patients undergoing surgery and the relatively limited number of geriatricians and hospitalists available to provide such services.

PROGRESS IN CHRONIC PAIN

See *New Frontiers,* pp. 36–37.

> ***Anes 35 (Level B)***: **The first priority in chronic pain trials is large cross-sectional studies that are powered to identify any relationship between pain intervention and functional outcomes.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Anes 35 should remain on the research agenda unchanged. Although efforts have been made to demonstrate improvements in functional status in elderly chronic pain patients that are related to opiate therapy (see Anes 36), there remains a need for hypothesis-generating studies that examine other therapies, including implantable spinal cord stimulators, pain blocks, physical and psychological rehabilitation therapy, and complementary therapies such as acupuncture.

> ***Anes 36 (Level A)***: **With the establishment of any relationship between intervention for chronic pain and functional outcomes in elderly patients (Anes 35), it must be determined prospectively if specific chronic pain therapies can improve functional outcomes in treatment groups relative to a historical or concurrent nonrandomized control.**

New Research Addressing This Question: Although no hypothesis-generating studies as suggested in Anes 35 have been published, there have been a number of reports examining the effects of pain intervention on functional outcome. Specifically, these studies evaluated the impact of opiate therapy. Eight studies [156–163] published since 2001 that enrolled a total of 2640 patients were included in a recent systematic review that included three other studies, for a total of 2877 patients. The quality of the included studies ranged from low to moderate or high, but overall, opiates were associated with significant improvements in functional status, including quality of life. [164]

No studies examining functional status outcomes as they relate to other pain management strategies in elderly patients were identified.

Modification of This Question in Light of New Research: Further studies are needed and should be based on outcomes from studies to address Anes 35. Here, too, a variety of therapeutic modalities should be examined.

> ***Anes 37 (Level C)***: **Given the high incidence rate of herpes zoster in the geriatric population, further prospective studies are needed to determine if antiviral, analgesic, or anti-inflammatory therapies during acute zoster can reduce, relative to standard care, the development of chronic postherpetic neuralgia.**

New Research Addressing This Question: Postherpetic neuralgia (PHN) is common in the elderly age group. [165,166] The pain associated with it is associated with significant functional disability. [167] Thus, studies aimed at the prevention of PHN have considerable public health significance.

The literature search did not identify any trials published since *New Frontiers* comparing the use of antiviral therapy versus standard care for the prevention of PHN. A systematic review concluded that oral acyclovir provided a modest reduction in pain 1 to 3 months after zoster onset. [168]

No studies exploring the use of steroids and analgesics were identified.

For theoretical reasons, combination therapy may be more effective in preventing PHN. Pasqualucci et al randomized 600 patients with acute herpes zoster to receive either intravenous acyclovir for 9 days combined with prednisolone for 21 days or epidural bupivacaine (boluses given every 6 to 12 hours) combined with epidural prednisolone every 3 to 4 days. Treatment duration in the epidural group ranged from 7 to 21 days. The incidence of PHN pain at 1 year was 22.2% and 1.6% in the acyclovir and epidural groups, respectively ($P < .001$). [169]

Because this approach requires hospitalization and extensive use of health care resources, van Wijck et al compared oral antivirals and analgesics with a single epidural injection of methylprednisolone and bupivacaine. Although the incidence of pain at 1 month was modestly reduced in the epidural group (48% versus 58%, relative risk 0.38, 95% CI: 0.71 to 0.97, $P = .02$), there were no differences at 3 and 6 months. [170]

A more recent approach to the prevention of PHN is the use of vaccines. With age, there is a progressive decline in cell-mediated immunity to varicella zoster virus; the incidence and severity of herpes zoster and PHN are associated with this decline. [171–179] That recurrence of herpes zoster is rare in immunocompetent individuals, presumably as a result of an immunizing effect, suggests that strategies to increase cell-mediated immunity would be useful in the prevention of PHN. [171–173,180,181]

In a multicenter randomized, double-blind, and placebo-controlled trial of over 38,000 patients aged 60 years and older, Oxman et al tested an investigational live attenuated varicella zoster vaccine for the prevention of PHN. The results were promising. In patients who received the vaccine, the herpes zoster and PHN were reduced by 51.3% and 66.5%, respectively (for both $P < .001$). There was a low incidence of side effects. [182]

Modification of This Question in Light of New Research: Given the lack of definitive answers regarding other strategies for its prevention, there remains a need for further prospective studies examining the role of antiviral, analgesic, and anti-inflammatory therapies during acute zoster in the prevention of PHN. Special consideration should be given to combination therapies and examining resource utilization. Moreover, Anes 37 should be designated as an A-level agenda item because PHN is both common and associated with significant functional disability among older persons.

As promising as vaccines may be for the prevention of PHN, in their current form they are not 100% effective in preventing PHN. Clearly, more research regarding this therapy is needed.

***Anes 38 (Level D)*: Cross-sectional studies documenting the association of chronic pain therapy with the incidence of complications like confusion, postural hypotension, falls, urinary retention, and constipation in the elderly population are needed.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Elderly persons have diminished physiologic functional reserve that affects all organ systems. (See *New Frontiers,* pp. 17–18.) This makes them more prone to adverse side effects from chronic pain treatment modalities. Information provided by Anes 38 will allow for more rational approach to treatment decision making. This is analogous to the possibility of using functional status to assist in surgical planning (see Anes 6). For example, patients with a high propensity for confusion may not be appropriate candidates for chronic opiate therapy.

***Anes 39 (Level D)*: Cross-sectional studies that describe pain management in cognitively impaired patients, relative to a nonimpaired population, are needed.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Anes 39 should remain unaltered. Given the diminished functional reserve capacity in cognitively impaired patients and potential for pain therapies (eg, opiates) to alter cognitive function, this question remains vital.

***Anes 40 (Level D)*: Pain assessment tools for chronic pain in the cognitively impaired elderly patient must be compared prospectively with standard assessment methods.**

New Research Addressing This Question: No research published since the initial literature review was found.

Modification of This Question in Light of New Research: Assessment of chronic pain includes evaluating the effects of pain, including functional status and altered mood. However, in chronic pain clinical practice and research, the same tools used to assess acute pain are used for chronic pain. Therefore, information derived in Anes 28 could be applied to Anes 40.

***Anes 41 (Level C)*: Prospective trials comparing different analgesic strategies with regard to clinical and functional outcomes are needed.**

New Research Addressing This Question: A study by Wong et al is an example of the usefulness of the research proposed in Anes 41. In this prospective, randomized, double-blind trial, 100 patients with pancreatic cancer were assigned to receive either neurolytic celiac plexus block with systemic analgesic therapy as needed or optimized systemic analgesic therapy along with a sham block. Patients were followed for 1 year or until death. Pain control ($P \leq .01$) and quality of life ($P < .001$) improved 1 week after randomization in both groups, but there was a larger decrease in pain in those who received the block ($P = .005$). Pain control was better in the block group over time, as well ($P = .01$). However, opiate consumption, opiate side effects, and quality of life were similar between groups. There was no difference in survival between groups. [183]

Modification of This Question in Light of New Research: More studies, such as the one described but focusing on elderly patients, are needed across the spectrum of chronic pain

conditions and therapies. This is especially crucial because many current invasive and implantable pain therapies are costly. If they cannot be shown to confer significant clinical and functional benefit, there will be little justification for their use in treating elderly patients.

NEW HORIZONS IN GERIATRIC ANESTHESIA

Since publication of *New Frontiers*, two areas of study have emerged—one new, one old—that bear further research in geriatric patients.

PERIOPERATIVE GLUCOSE CONTROL

Diabetes mellitus is associated with adverse perioperative outcomes. [184–190] Even in patients without diabetes, hyperglycemia is associated with increased mortality, incidence of postoperative infection, and resource utilization in surgical patients. [191,192] Because of this, a number of recent studies have examined the role of glucose control in critically ill and surgical patients. [191,193–202] In 2001, van den Berghe et al published a landmark study examining the effect of intensive insulin therapy on mortality, morbidity, and resource utilization in critically ill patients. In this prospective study, patients admitted to a surgical intensive care unit were randomized to receive either intensive insulin therapy (maintenance of blood glucose between 80 and 110 mg/dL) or conventional treatment (insulin only for blood glucose $>$ 215 mg/dL and subsequent maintenance of blood glucose between 180 and 200 mg/dL). Overall, intensive care unit mortality was 4.6% and 8.0% ($P > .04$) in the intensive insulin and conventional treatment groups, respectively. The adjusted reduction in mortality was 32% (95% CI: 2% to 55%). [202] Intensive insulin therapy is associated with better immune system function, [203] reduced inflammation, [204] improved lipid profiles, [205] preservation of endothelial function, [206] and protected mitochondrial structure and function. [207] However, it appears that the clinical benefit of this therapy is due to blood glucose levels independently of insulin dose. [208,209]

Therefore, studies addressing the role of intra- and postoperative glucose management in elderly surgical patients are imperative. However, hypoglycemia is associated with mortality in elderly patients, [210] and the incidence of hypoglycemia is high with intensive insulin therapy. [202] Given that glucose would not likely be as well controlled outside of a study situation, [211] studies examining morbidity and mortality associated with various glucose levels should also address morbidity caused by strategies to lower perioperative glucose.

***Anes 42 (Level A)*: Large prospective randomized studies addressing the role of intraoperative and postoperative glucose management in elderly surgical patients are needed, to include assessment of associations of specific glucose levels or specific glucose control strategies with morbidity and mortality.**

REGIONAL VERSUS GENERAL ANESTHESIA

New Frontiers concluded that research on the impact of intraoperative anesthetic management on perioperative outcomes in the elderly was unlikely to be fruitful. (See *New Frontiers,* pp. 23–25.) Well-designed investigation into the effects on the perioperative outcomes of regional versus general anesthesia—arguably the most substantively dissimilar choices regarding intraoperative anesthetic management—failed to demonstrate clini-

cally significant differences in outcomes between the two techniques.[212] Given the equivalency in outcome between these two vastly different techniques, it was felt that further research into this area was unlikely to yield clinically useful information and should not be pursued, especially given limited funds for research. However, recent studies suggest that anesthetic management may indeed affect cognitive outcome.

For example, in vivo studies demonstrate that exposing neurons to volatile anesthetic gases increases oligomerization and toxicity of Alzheimer-like proteins.[213] Further, in an animal model, exposure to clinically relevant concentrations of volatile anesthetics leads to impaired memory and learning.[214–216]

Design issues may be why previous studies of regional versus general anesthesia failed to show differences in cognitive outcomes. In theory, the advantage of regional anesthetic techniques is that they minimize exposure to medications that act on the central nervous system and block the neuroendocrine stress response to surgery.[217] A major weakness of previous studies examining the effect of regional versus general anesthesia on cognitive outcomes was that postoperative analgesic management was not controlled.[135,218,219] Thus, patients were exposed to pharmacologic agents that may have affected cognitive outcomes (eg, opiates). It is possible that improvements in cognitive outcome related to anesthetic or analgesic technique require that those techniques be continued into the postoperative period. Recently, postoperative analgesic techniques have been developed which employ indwelling perineural catheters to deliver continuous infusions of local anesthetics. These techniques are associated with significant reductions in parenteral opiate requirements and excellent analgesia.[220] Preliminary evidence suggests that, by themselves, these techniques are associated with reduced incidence of postoperative delirium. In addition, these techniques may lead to improved cognitive outcomes when patients also receive regional instead of general anesthesia.[90]

In light of the development of peripheral nerve catheter techniques and these data, prospective randomized trials should be performed that examine the effect of intravenous patient-controlled opiate analgesia versus central neuraxial or peripheral nerve catheter analgesia, or both, on cognitive outcomes in the setting of both regional versus general anesthesia. These studies will be difficult and expensive to perform, but they are exceedingly important, as the results may have a profound impact on the perioperative care of elderly surgical patients.

***Anes 43 (Level A)*: Prospective randomized trials are needed to determine the effect of intravenous patient-controlled opiate analgesia versus central or peripheral nerve catheter analgesia, or both, on cognitive outcomes in the setting of both regional versus general anesthesia.**

REFERENCES

1. Tiret L, Desmonts JM, Hatton F, Vourc'h G. Complications associated with anaesthesia—a prospective survey in France. Can Anaesth Soc J 1986;33:336-344.
2. Cook DJ. Geriatric anesthesia. In Solomon DH, LoCicero J, 3rd, Rosenthal RA (eds): New Frontiers in Geriatrics Research: An Agenda for Surgical and Related Medical Specialties. New York: American Geriatrics Society, 2004, pp. 9-52 (online at http://www.frycomm.com/ags/rasp).
3. Hilditch WG, Asbury AJ, Jack E, McGrane S. Validation of a pre-anaesthetic screening questionnaire. Anaesthesia 2003;58:874-877.

4. van Klei WA, Hennis PJ, Moen J, et al. The accuracy of trained nurses in pre-operative health assessment: results of the OPEN study. Anaesthesia 2004;59:971-978.
5. Gibbs J, Cull W, Henderson W, et al. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. Arch Surg 1999;134:36-42.
6. Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. N Engl J Med 1991;325:525-532.
7. Guigoz Y, Vellas BJ. [Malnutrition in the elderly: the Mini Nutritional Assessment (MNA)]. Ther Umsch 1997;54:345-350.
8. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: the Mini Nutritional Assessment as part of the geriatric evaluation. Nutr Rev 1996;54:S59-S65.
9. Cohendy R, Gros T, Arnaud-Battandier F, et al. Preoperative nutritional evaluation of elderly patients: the Mini Nutritional Assessment as a practical tool. Clin Nutr 1999;18:345-348.
10. Rubenstein LZ, Harker JO, Salva A, et al. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci 2001;56:M366-M372.
11. Cohendy R, Rubenstein LZ, Eledjam JJ. The Mini Nutritional Assessment-Short Form for preoperative nutritional evaluation of elderly patients. Aging (Milano) 2001;13:293-297.
12. Leung JM, Dzankic S. Relative importance of preoperative health status versus intraoperative factors in predicting postoperative adverse outcomes in geriatric surgical patients. J Am Geriatr Soc 2001;49:1080-1085.
13. Jankowski CJ, Cook DJ, Schroeder DR, Warner DO. Mild reductions in preoperative cognitive and functional status are associated with postoperative delirium [abstract]. Anesth Analg 2005;100:S178.
14. Law WL, Chu KW, Tung PH. Laparoscopic colorectal resection: a safe option for elderly patients. J Am Coll Surg 2002;195:768-773.
15. Pompei P, Foreman M, Rudberg MA, et al. Delirium in hospitalized older persons: outcomes and predictors. J Am Geriatr Soc 1994;42:809-815.
16. Inouye SK, Viscoli CM, Horwitz RI, et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 1993;119:474-481.
17. Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994;271:134-139.
18. Taylor KI, Salmon DP, Rice VA, et al. Longitudinal examination of American National Adult Reading Test (AMNART) performance in dementia of the Alzheimer type (DAT): validation and correction based on degree of cognitive decline. J Clin Exp Neuropsychol 1996;18:883-891.
19. Folstein MF, Robins LN, Helzer JE. The Mini-Mental State Examination. Arch Gen Psychiatry 1983;40:812.
20. Loonstra AS, Tarlow AR, Sellers AH. COWAT metanorms across age, education, and gender. Appl Neuropsychol 2001;8:161-166.
21. Steinberg BA, Bieliauskas LA, Smith GE, et al. Mayo's Older Americans Normative Studies: Age- and IQ-Adjusted Norms for the Auditory Verbal Learning Test and the Visual Spatial Learning Test. Clin Neuropsychol 2005;19:464-523.
22. Jensen AR, Rohwer WD, Jr. The Stroop color-word test: a review. Acta Psychol (Amst) 1966;25:36-93.
23. Gruber-Baldini AL, Zimmerman S, Morrison RS, et al. Cognitive impairment in hip fracture patients: timing of detection and longitudinal follow-up. J Am Geriatr Soc 2003;51:1227-1236.
24. Liberto JG, Oslin DW, Ruskin PE. Alcoholism in older persons: a review of the literature. Hosp Community Psychiatry 1992;43:975-984.

25. Rocca WA, Grossardt BR, Peterson BJ, et al. The Mayo Clinic cohort study of personality and aging: design and sampling, reliability and validity of instruments, and baseline description. Neuroepidemiology 2006;26:119-129.
26. Licht-Strunk E, van der Kooij KG, van Schaik DJ, et al. Prevalence of depression in older patients consulting their general practitioner in The Netherlands. Int J Geriatr Psychiatry 2005;20:1013-1019.
27. Ostbye T, Kristjansson B, Hill G, et al. Prevalence and predictors of depression in elderly Canadians: The Canadian Study of Health and Aging. Chronic Dis Can 2005;26:93-99.
28. Harris T, Cook DG, Victor C, et al. Onset and persistence of depression in older people—results from a 2-year community follow-up study. Age Ageing 2006;35:25-32.
29. Hybels CF, Blazer DG. Epidemiology of late-life mental disorders. Clin Geriatr Med 2003;19:663-696, v.
30. Blazer DG. Depression in late life: review and commentary. J Gerontol A Biol Sci Med Sci 2003;58:M249-M265.
31. Mangano DT. Aspirin and mortality from coronary bypass surgery. N Engl J Med 2002;347:1309-1317.
32. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. Anesthesiology 1998;88:7-17.
33. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996;335:1713-1720.
34. Poldermans D, Boersma E, Bax JJ, et al. Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery. Eur Heart J 2001;22:1353-1358.
35. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999;341:1789-1794.
36. Lindenauer PK, Pekow P, Wang K, et al. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 2005;353:349-361.
37. Devereaux PJ, Yusuf S, Yang H, et al. Are the recommendations to use perioperative beta-blocker therapy in patients undergoing noncardiac surgery based on reliable evidence? CMAJ 2004;171:245-247.
38. Schouten O, Poldermans D, Visser L, et al. Fluvastatin and bisoprolol for the reduction of perioperative cardiac mortality and morbidity in high-risk patients undergoing non-cardiac surgery: rationale and design of the DECREASE-IV study. Am Heart J 2004;148:1047-1052.
39. Silverstein JH. Personal communication (study in progress): Elder surgery—functional recovery after beta blockade. NIH Grant #5R01AG018772-05. Abstract available at http://crisp.cit.nih.gov.
40. Brotman DJ, Jaffer AK, Hurbanek JG, Morra N. Warfarin prophylaxis and venous thromboembolism in the first 5 days following hip and knee arthroplasty. Thromb Haemost 2004;92:1012-1017.
41. Cook G, Depares J, Singh M, McElduff P. Readmission after hysterectomy and prophylactic low molecular weight heparin: retrospective case-control study. BMJ 2006;332:819-820.
42. Gonzalez Della Valle A, Serota A, Go G, et al. Venous thromboembolism is rare with a multimodal prophylaxis protocol after total hip arthroplasty. Clin Orthop Relat Res 2006;444:146-153.
43. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med 2005;165:1095-1106.

44. Tsen LC, Segal S, Pothier M, Bader AM. Alternative medicine use in presurgical patients. Anesthesiology 2000;93:148-151.
45. Hodges PJ, Kam PC. The peri-operative implications of herbal medicines. Anaesthesia 2002;57:889-899.
46. Ettema HB, Hoppener MR, Henny CP, et al. Compliance of Dutch orthopedic departments with national guidelines on thromboprophylaxis: a survey of Dutch orthopedic thromboprophylaxis. Acta Orthop 2005;76:99-103.
47. Kucher N, Koo S, Quiroz R, et al. Electronic alerts to prevent venous thromboembolism among hospitalized patients. N Engl J Med 2005;352:969-977.
48. Mosen D, Elliott CG, Egger MJ, et al. The effect of a computerized reminder system on the prevention of postoperative venous thromboembolism. Chest 2004;125:1635-1641.
49. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology 2006;105:198-208. Online at: http://www.asahq.org/publicationsAndServices/BCTGuidesFinal.pdf.
50. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 2001;49:516-522.
51. Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001;345:1305-1310.
52. Eriksson BI, Agnelli G, Cohen AT, et al. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. J Thromb Haemost 2003;1:2490-2496.
53. Francis CW, Berkowitz SD, Comp PC, et al. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. N Engl J Med 2003;349:1703-1712.
54. Colwell CW, Jr., Berkowitz SD, Davidson BL, et al. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement: a randomized, double-blind study. J Thromb Haemost 2003;1:2119-2130.
55. Eriksson BI, Bergqvist D, Kalebo P, et al. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. Lancet 2002;360:1441-1447.
56. Eriksson BI, Dahl OE, Buller HR, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. J Thromb Haemost 2005;3:103-111.
57. Agnelli G, Bergqvist D, Cohen AT, et al. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg 2005;92:1212-1220.
58. Eriksson BI, Borris L, Dahl OE, et al. Oral, direct factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. J Thromb Haemost 2006;4:121-128.
59. Turpie AG, Fisher WD, Bauer KA, et al. BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. J Thromb Haemost 2005;3:2479-2486.
60. Samama CM, Vray M, Barre J, et al. Extended venous thromboembolism prophylaxis after total hip replacement: a comparison of low-molecular-weight heparin with oral anticoagulant. Arch Intern Med 2002;162:2191-2196.

61. Scott EM, Leaper DJ, Clark M, Kelly PJ. Effects of warming therapy on pressure ulcers—a randomized trial. AORN J 2001;73:921-927, 929-933, 936-938.
62. Yucel Y, Barlan M, Lenhardt R, et al. Perioperative hypothermia does not enhance the risk of cancer dissemination. Am J Surg 2005;189:651-655.
63. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med 1996;334:1209-1215.
64. Just B, Delva E, Camus Y, Lienhart A. Oxygen uptake during recovery following naloxone: relationship with intraoperative heat loss. Anesthesiology 1992;76:60-64.
65. Frank SM, Fleisher LA, Breslow MJ, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: a randomized clinical trial. JAMA 1997;277:1127-1134.
66. Schmied H, Kurz A, Sessler DI, et al. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. Lancet 1996;347:289-292.
67. Carli F, Emery PW, Freemantle CA. Effect of perioperative normothermia on postoperative protein metabolism in elderly patients undergoing hip arthroplasty. Br J Anaesth 1989;63:276-282.
68. Sessler DI, Sessler AM. Experimental determination of heat flow parameters during induction of general anesthesia. Anesthesiology 1998;89:657-665.
69. Macario A, Dexter F. What are the most important risk factors for a patient's developing intraoperative hypothermia? Anesth Analg 2002;94:215-220, table of contents.
70. Zanetti G, Giardina R, Platt R. Intraoperative redosing of cefazolin and risk for surgical site infection in cardiac surgery. Emerg Infect Dis 2001;7:828-831.
71. Martone WJ, Nichols RL. Recognition, prevention, surveillance, and management of surgical site infections: introduction to the problem and symposium overview. Clin Infect Dis 2001;33 Suppl 2:S67-S68.
72. Posacioglu H, Apaydin AZ, Islamoglu F, et al. Adverse effects of cell saver in patients undergoing ruptured abdominal aortic aneurysm repair. Ann Vasc Surg 2002;16:450-455.
73. Tang R, Chen HH, Wang YL, et al. Risk factors for surgical site infection after elective resection of the colon and rectum: a single-center prospective study of 2,809 consecutive patients. Ann Surg 2001;234:181-189.
74. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. N Engl J Med 2006;354:379-386.
75. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: a report by the American Society of Anesthesiologist Task Force on Preoperative Fasting. Anesthesiology 1999;90:896-905. Online at: http://www.asahq.org/publicationsAndServices/NPO.pdf.
76. Thomas DR, Tariq SH, Makhdomm S, et al. Physician misdiagnosis of dehydration in older adults. J Am Med Dir Assoc 2003;4:251-254.
77. Volkert D, Kreuel K, Stehle P. Fluid intake of community-living, independent elderly in Germany—a nationwide, representative study. J Nutr Health Aging 2005;9:305-309.
78. Bennett JA, Thomas V, Riegel B. Unrecognized chronic dehydration in older adults: examining prevalence rate and risk factors. J Gerontol Nurs 2004;30:22-28; quiz 52-53.
79. de Larminat V, Montravers P, Dureuil B, Desmonts JM. Alteration in swallowing reflex after extubation in intensive care unit patients. Crit Care Med 1995;23:486-490.
80. Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med 2001;344:665-671.
81. Warner DO. Preventing postoperative pulmonary complications: the role of the anesthesiologist. Anesthesiology 2000;92:1467-1472.

82. Lawrence VA, Hilsenbeck SG, Mulrow CD, et al. Incidence and hospital stay for cardiac and pulmonary complications after abdominal surgery. J Gen Intern Med 1995;10:671-678.
83. Bixler EO, Vgontzas AN, Ten Have T, et al. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med 1998;157:144-148.
84. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217-1239.
85. Gali B, Plevak DJ, Morganthaler T, Gay P. Identification and perioperative management of patients presumed at risk for obstructive sleep apnea. [abstract #0599]. Sleep 2005;28:A202.
86. Frasco PE, Sprung J, Trentman TL. The impact of the joint commission for accreditation of healthcare organizations pain initiative on perioperative opiate consumption and recovery room length of stay. Anesth Analg 2005;100:162-168.
87. Curtiss CP. JCAHO: meeting the standards for pain management. Orthop Nurs 2001;20:27-30, 41.
88. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology 1997;86:24-33.
89. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 1987;240:159-166.
90. Jankowski CJ, Cook DJ, Trenerry MR, et al. Continuous peripheral nerve block analgesia and central neuraxial anesthesia are associated with reduced incidence of postoperative delirium in the elderly [abstract]. Anesthesiology 2005;103:A1467.
91. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg 2004;98:153-158, table of contents.
92. Cortinez LI, Hsu YW, Sum-Ping ST, et al. Dexmedetomidine pharmacodynamics: Part II: Crossover comparison of the analgesic effect of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology 2004;101:1077-1083.
93. Marzinski LR. The tragedy of dementia: clinically assessing pain in the confused nonverbal elderly. J Gerontol Nurs 1991;17:25-28.
94. Merskey H, Bogduk M. Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Syndromes. Seattle, WA: IASP Press, 1994.
95. Krulewitch H, London MR, Skakel VJ, et al. Assessment of pain in cognitively impaired older adults: a comparison of pain assessment tools and their use by nonprofessional caregivers. J Am Geriatr Soc 2000;48:1607-1611.
96. DOLOPLUS 2: behavioral pain assessment scale for elderly subjects presenting with verbal communication disorders. 2001. Accessed: March 2, 2006. Online at http://www.doloplus.com/versiongb/index.htm.
97. Lefebvre-Chapiro S. The Doloplus 2 scale—evaluating pain in the elderly. Eur J Palliat Care 2001;8:191-194.
98. Warden V, Hurley AC, Volicer L. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. J Am Med Dir Assoc 2003;4:9-15.
99. Stolee P, Hillier LM, Esbaugh J, et al. Instruments for the assessment of pain in older persons with cognitive impairment. J Am Geriatr Soc 2005;53:319-326.
100. Fisher SE, Burgio LD, Thorn BE, et al. Pain assessment and management in cognitively impaired nursing home residents: Association of Certified Nursing Assistant pain report, Minimum Data Set pain report, and analgesic medication use. J Am Geriatr Soc 2002;50:152-156.
101. Lawton MP, Casten R, Parmelee PA, et al. Psychometric characteristics of the minimum data set II: validity. J Am Geriatr Soc 1998;46:736-744.
102. Casten R, Lawton MP, Parmelee PA, Kleban MH. Psychometric characteristics of the minimum data set I: confirmatory factor analysis. J Am Geriatr Soc 1998;46:726-735.

103. Cohen-Mansfield J. The adequacy of the minimum data set assessment of pain in cognitively impaired nursing home residents. J Pain Symptom Manage 2004;27:343-351.
104. Villanueva MR, Smith TL, Erickson JS, et al. Pain Assessment for the Dementing Elderly (PADE): reliability and validity of a new measure. J Am Med Dir Assoc 2003;4:1-8.
105. Lynch EP, Lazor MA, Gellis JE, et al. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg 1998;86:781-785.
106. Thoren T, Sundberg A, Wattwil M, et al. Effects of epidural bupivacaine and epidural morphine on bowel function and pain after hysterectomy. Acta Anaesthesiol Scand 1989;33:181-185.
107. Scheinin B, Asantila R, Orko R. The effect of bupivacaine and morphine on pain and bowel function after colonic surgery. Acta Anaesthesiol Scand 1987;31:161-164.
108. Liu S, Angel JM, Owens BD, et al. Effects of epidural bupivacaine after thoracotomy. Reg Anesth 1995;20:303-310.
109. Liu SS, Carpenter RL, Mackey DC, et al. Effects of perioperative analgesic technique on rate of recovery after colon surgery. Anesthesiology 1995;83:757-765.
110. Gelman S, Feigenberg Z, Dintzman M, Levy E. Electroenterography after cholecystectomy: the role of high epidural analgesia. Arch Surg 1977;112:580-583.
111. Bonica JJ. The Management of Pain. Philadelphia, PA: Lea & Febiger, 1953.
112. DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. Anesth Analg 1998;86:102-106.
113. Cadogan MP. Assessing pain in cognitively impaired nursing home residents: the state of the science and the state we're in. J Am Med Dir Assoc 2003;4:50-51.
114. Simons LA, Tett S, Simons J, et al. Multiple medication use in the elderly: use of prescription and non-prescription drugs in an Australian community setting. Med J Aust 1992;157:242-246.
115. Stewart RB, Moore MT, May FE, et al. A longitudinal evaluation of drug use in an ambulatory elderly population. J Clin Epidemiol 1991;44:1353-1359.
116. Jankowski CJ. Personal communication. 2005.
117. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941-948.
118. Sharma PT, Sieber FE, Zakriya KJ, et al. Recovery room delirium predicts postoperative delirium after hip-fracture repair. Anesth Analg 2005;101:1215-1220, table of contents.
119. Marcantonio E, Ta T, Duthie E, Resnick NM. Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. J Am Geriatr Soc 2002;50:850-857.
120. Zakriya KJ, Christmas C, Wenz JF, Sr., et al. Preoperative factors associated with postoperative change in confusion assessment method score in hip fracture patients. Anesth Analg 2002;94:1628-1632, table of contents.
121. Galanakis P, Bickel H, Gradinger R, et al. Acute confusional state in the elderly following hip surgery: incidence, risk factors and complications. Int J Geriatr Psychiatry 2001;16:349-355.
122. Kudoh A, Takahira Y, Katagai H, Takazawa T. Small-dose ketamine improves the postoperative state of depressed patients. Anesth Analg 2002;95:114-118, table of contents.
123. Clayer M, Bruckner J. Occult hypoxia after femoral neck fracture and elective hip surgery. Clin Orthop Relat Res 2000:265-271.
124. Brauer C, Morrison RS, Silberzweig SB, Siu AL. The cause of delirium in patients with hip fracture. Arch Intern Med 2000;160:1856-1860.
125. Zakriya K, Sieber FE, Christmas C, et al. Brief postoperative delirium in hip fracture patients affects functional outcome at three months. Anesth Analg 2004;98:1798-1802, table of contents.
126. Shigeta H, Yasui A, Nimura Y, et al. Postoperative delirium and melatonin levels in elderly patients. Am J Surg 2001;182:449-454.

127. Kagansky N, Rimon E, Naor S, et al. Low incidence of delirium in very old patients after surgery for hip fractures. Am J Geriatr Psychiatry 2004;12:306-314.
128. Kudoh A, Takase H, Takahira Y, Takazawa T. Postoperative confusion increases in elderly long-term benzodiazepine users. Anesth Analg 2004;99:1674-1678, table of contents.
129. Formiga F, Lopez-Soto A, Sacanella E, et al. Mortality and morbidity in nonagenarian patients following hip fracture surgery. Gerontology 2003;49:41-45.
130. Bickel H, Gradinger R, Kochs E, et al. [Incidence and risk factors of delirium after hip surgery]. Psychiatr Prax 2004;31:360-365.
131. Agnoletti V, Ansaloni L, Catena F, et al. Postoperative delirium after elective and emergency surgery: analysis and checking of risk factors: a study protocol. BMC Surg 2005;5:12.
132. Kudoh A, Katagai H, Takase H, Takazawa T. Effect of preoperative discontinuation of antipsychotics in schizophrenic patients on outcome during and after anaesthesia. Eur J Anaesthesiol 2004;21:414-416.
133. Adunsky A, Levy R, Heim M, et al. Meperidine analgesia and delirium in aged hip fracture patients. Arch Gerontol Geriatr 2002;35:253-259.
134. Liptzin B, Laki A, Garb JL, et al. Donepezil in the prevention and treatment of post-surgical delirium. Am J Geriatr Psychiatry 2005;13:1100-1106.
135. Marcantonio ER, Goldman L, Orav EJ, et al. The association of intraoperative factors with the development of postoperative delirium. Am J Med 1998;105:380-384.
136. Milisen K, Foreman MD, Abraham IL, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. J Am Geriatr Soc 2001;49:523-532.
137. Jankowski CJ, Keegan MT, Bolton CF, Harrison BA. Neuropathy following axillary brachial plexus block: is it the tourniquet? Anesthesiology 2003;99:1230-1232.
138. Breitbart W, Rosenfeld B, Roth A, et al. The Memorial Delirium Assessment Scale. J Pain Symptom Manage 1997;13:128-137.
139. Gaudreau JD, Gagnon P, Harel F, et al. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. J Pain Symptom Manage 2005;29:368-375.
140. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res 1988;23:89-97.
141. Adamis D, Treloar A, MacDonald AJ, Martin FC. Concurrent validity of two instruments (the Confusion Assessment Method and the Delirium Rating Scale) in the detection of delirium among older medical inpatients. Age Ageing 2005;34:72-75.
142. McNicoll L, Pisani MA, Ely EW, et al. Detection of delirium in the intensive care unit: comparison of confusion assessment method for the intensive care unit with confusion assessment method ratings. J Am Geriatr Soc 2005;53:495-500.
143. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. Res Theory Nurs Pract 2003;17:31-50.
144. McCusker J, Cole MG, Dendukuri N, Belzile E. The delirium index, a measure of the severity of delirium: new findings on reliability, validity, and responsiveness. J Am Geriatr Soc 2004;52:1744-1749.
145. Buschke H, Kuslansky G, Katz M, et al. Screening for dementia with the memory impairment screen. Neurology 1999;52:231-238.
146. Teng EL, Hasegawa K, Homma A, et al. The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. Int Psychogeriatr 1994;6:45-58; discussion 62.
147. Leopold NA, Borson AJ. An alphabetical 'WORLD'. A new version of an old test. Neurology 1997;49:1521-1524.
148. Watson YI, Arfken CL, Birge SJ. Clock completion: an objective screening test for dementia. J Am Geriatr Soc 1993;41:1235-1240.

149. Lorentz WJ, Scanlan JM, Borson S. Brief screening tests for dementia. Can J Psychiatry 2002;47:723-733.
150. Borson S, Scanlan J, Brush M, et al. The Mini-Cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry 2000;15:1021-1027.
151. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. J Am Geriatr Soc 2003;51:1451-1454.
152. Neelon VJ, Champagne MT, Carlson JR, Funk SG. The NEECHAM Confusion Scale: construction, validation, and clinical testing. Nurs Res 1996;45:324-330.
153. Albert MS, Levkoff SE, Reilly C, et al. The delirium symptom interview: an interview for the detection of delirium symptoms in hospitalized patients. J Geriatr Psychiatry Neurol 1992;5:14-21.
154. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968;114:797-811.
155. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc 2005;53:1658-1666.
156. Allan L, Hays H, Jensen NH, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ 2001;322:1154-1158.
157. Allan L, Richarz U, Simpson K, Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. Spine 2005;30:2484-2490.
158. Babul N, Noveck R, Chipman H, et al. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. J Pain Symptom Manage 2004;28:59-71.
159. Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. Pain 2003;104:323-331.
160. Franco ML, Seoane A, Franco ML. Usefulness of transdermal fentanyl in the management of nonmalignant chronic pain: a prospective, observational, multicenter study. Pain Clinic 2002;14:99-112.
161. Milligan K, Lanteri-Minet M, Borchert K, et al. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. J Pain 2001;2:197-204.
162. Mystakidou K, Parpa E, Tsilika E, et al. Long-term management of noncancer pain with transdermal therapeutic system-fentanyl. J Pain 2003;4:298-306.
163. Tassain V, Attal N, Fletcher D, et al. Long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. Pain 2003;104:389-400.
164. Devulder J, Richarz U, Nataraja SH. Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. Curr Med Res Opin 2005;21:1555-1568.
165. Portenoy RK, Duma C, Foley KM. Acute herpetic and postherpetic neuralgia: clinical review and current management. Ann Neurol 1986;20:651-664.
166. Stankus SJ, Dlugopolski M, Packer D. Management of herpes zoster (shingles) and postherpetic neuralgia. Am Fam Physician 2000;61:2437-2444, 2447-2438.
167. Oster G, Harding G, Dukes E, et al. Pain, medication use, and health-related quality of life in older persons with postherpetic neuralgia: results from a population-based survey. J Pain 2005;6:356-363.
168. Alper BS, Lewis PR. Does treatment of acute herpes zoster prevent or shorten postherpetic neuralgia? J Fam Pract 2000;49:255-264.

169. Pasqualucci A, Pasqualucci V, Galla F, et al. Prevention of post-herpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone. Acta Anaesthesiol Scand 2000;44:910-918.
170. van Wijck AJ, Opstelten W, Moons KG, et al. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. Lancet 2006;367:219-224.
171. Weller TH. Varicella and herpes zoster: changing concepts of the natural history, control, and importance of a not-so-benign virus. N Engl J Med 1983;309:1434-1440.
172. Ragozzino MW, Melton LJ, 3rd, Kurland LT, et al. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore) 1982;61:310-316.
173. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med 1995;155:1605-1609.
174. Choo PW, Galil K, Donahue JG, et al. Risk factors for postherpetic neuralgia. Arch Intern Med 1997;157:1217-1224.
175. Galil K, Choo PW, Donahue JG, Platt R. The sequelae of herpes zoster. Arch Intern Med 1997;157:1209-1213.
176. Miller AE. Selective decline in cellular immune response to varicella-zoster in the elderly. Neurology 1980;30:582-587.
177. Berger R, Florent G, Just M. Decrease of the lymphoproliferative response to varicella-zoster virus antigen in the aged. Infect Immun 1981;32:24-27.
178. Burke BL, Steele RW, Beard OW, et al. Immune responses to varicella-zoster in the aged. Arch Intern Med 1982;142:291-293.
179. Levin MJ, Murray M, Rotbart HA, et al. Immune response of elderly individuals to a live attenuated varicella vaccine. J Infect Dis 1992;166:253-259.
180. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Med 1965;58:9-20.
181. Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. Neurology 1995;45:S41-S46.
182. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352:2271-2284.
183. Wong GY, Schroeder DR, Carns PE, et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA 2004;291:1092-1099.
184. Zerr KJ, Furnary AP, Grunkemeier GL, et al. Glucose control lowers the risk of wound infection in diabetics after open heart operations. Ann Thorac Surg 1997;63:356-361.
185. Latham R, Lancaster AD, Covington JF, et al. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. Infect Control Hosp Epidemiol 2001;22:607-612.
186. Pomposelli JJ, Baxter JK, 3rd, Babineau TJ, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. JPEN J Parenter Enteral Nutr 1998;22:77-81.
187. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2002;105:1257-1267.
188. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 1977;297:845-850.
189. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. Diabetes Care 1999;22:1408-1414.

190. Guvener M, Pasaoglu I, Demircin M, Oc M. Perioperative hyperglycemia is a strong correlate of postoperative infection in type II diabetic patients after coronary artery bypass grafting. Endocr J 2002;49:531-537.
191. Gandhi GY, Nuttall GA, Abel MD, et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. Mayo Clin Proc 2005;80:862-866.
192. Bochicchio GV, Salzano L, Joshi M, et al. Admission preoperative glucose is predictive of morbidity and mortality in trauma patients who require immediate operative intervention. Am Surg 2005;71:171-174.
193. Lazar HL, Philippides G, Fitzgerald C, et al. Glucose-insulin-potassium solutions enhance recovery after urgent coronary artery bypass grafting. J Thorac Cardiovasc Surg 1997;113:354-360; discussion 360-352.
194. Besogul Y, Tunerir B, Aslan R, et al. Clinical, biochemical and histochemical assessment of pretreatment with glucose-insulin-potassium for patients undergoing mitral valve replacement in the third and fourth functional groups of the New York Heart Association. Cardiovasc Surg 1999;7:645-650.
195. Lazar HL, Chipkin S, Philippides G, et al. Glucose-insulin-potassium solutions improve outcomes in diabetics who have coronary artery operations. Ann Thorac Surg 2000;70:145-150.
196. Szabo Z, Arnqvist H, Hakanson E, et al. Effects of high-dose glucose-insulin-potassium on myocardial metabolism after coronary surgery in patients with Type II diabetes. Clin Sci (Lond) 2001;101:37-43.
197. Ulgen MS, Alan S, Akdemir O, Toprak N. The effect of glucose-insulin-potassium solution on ventricular late potentials and heart rate variability in acute myocardial infarction. Coron Artery Dis 2001;12:507-512.
198. Groban L, Butterworth J, Legault C, et al. Intraoperative insulin therapy does not reduce the need for inotropic or antiarrhythmic therapy after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2002;16:405-412.
199. Lell WA, Nielsen VG, McGiffin DC, et al. Glucose-insulin-potassium infusion for myocardial protection during off-pump coronary artery surgery. Ann Thorac Surg 2002;73:1246-1251; discussion 1251-1242.
200. Rao V, Christakis GT, Weisel RD, et al. The insulin cardioplegia trial: myocardial protection for urgent coronary artery bypass grafting. J Thorac Cardiovasc Surg 2002;123:928-935.
201. Smith A, Grattan A, Harper M, et al. Coronary revascularization: a procedure in transition from on-pump to off-pump? The role of glucose-insulin-potassium revisited in a randomized, placebo-controlled study. J Cardiothorac Vasc Anesth 2002;16:413-420.
202. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345:1359-1367.
203. Weekers F, Giulietti AP, Michalaki M, et al. Metabolic, endocrine, and immune effects of stress hyperglycemia in a rabbit model of prolonged critical illness. Endocrinology 2003;144:5329-5338.
204. Hansen TK, Thiel S, Wouters PJ, et al. Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. J Clin Endocrinol Metab 2003;88:1082-1088.
205. Mesotten D, Swinnen JV, Vanderhoydonc F, et al. Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy. J Clin Endocrinol Metab 2004;89:219-226.
206. Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. J Clin Invest 2005;115:2277-2286.
207. Vanhorebeek I, De Vos R, Mesotten D, et al. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. Lancet 2005;365:53-59.

208. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA 2003;290:2041-2047.
209. van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med 2003;31:359-366.
210. Kagansky N, Levy S, Rimon E, et al. Hypoglycemia as a predictor of mortality in hospitalized elderly patients. Arch Intern Med 2003;163:1825-1829.
211. Murrary MJ, Brull SJ, Coursin DB. Strict blood glucose control in the ICU: panacea or Pandora's box? J Cardiothorac Vasc Anesth 2004;18:687-689.
212. Norris EJ, Beattie C, Perler BA, et al. Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. Anesthesiology 2001;95:1054-1067.
213. Eckenhoff RG, Johansson JS, Wei H, et al. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. Anesthesiology 2004;101:703-709.
214. Culley DJ, Baxter MG, Crosby CA, et al. Impaired acquisition of spatial memory 2 weeks after isoflurane and isoflurane-nitrous oxide anesthesia in aged rats. Anesth Analg 2004;99:1393-1397; table of contents.
215. Culley DJ, Baxter MG, Yukhananov R, Crosby G. Long-term impairment of acquisition of a spatial memory task following isoflurane-nitrous oxide anesthesia in rats. Anesthesiology 2004;100:309-314.
216. Culley DJ, Baxter M, Yukhananov R, Crosby G. The memory effects of general anesthesia persist for weeks in young and aged rats. Anesth Analg 2003;96:1004-1009, table of contents.
217. Kehlet H. Modifications of responses to surgery by neural blockade. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain. Philadelphia, PA: Lippincott-Raven, 1998, pp. 129-175.
218. Rasmussen LS, Johnson T, Kuipers HM, et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003;47:260-266.
219. Williams-Russo P, Sharrock NE, Mattis S, et al. Cognitive effects after epidural vs general anesthesia in older adults: a randomized trial. JAMA 1995;274:44-50.
220. Capdevila X, Coimbra C, Choquet O. Approaches to the lumbar plexus: success, risks, and outcome. Reg Anesth Pain Med 2005;30:150-162.